

FORM PTO-1390
(REV 10-95)

U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

ATTORNEY'S DOCKET NUMBER

**TRANSMITTAL LETTER TO THE UNITED STATES
DESIGNATED/ELECTED OFFICE (DO/EO/US)
CONCERNING A FILING UNDER 35 U.S.C. §371**

MERCK 2338

U.S. APPLICATION NO. (If known, see 37 CFR §1.5)

10/018482

INTERNATIONAL APPLICATION NO.

INTERNATIONAL FILING DATE

PCT/EP00/05456

14 June 2000

PRIORITY DATE CLAIMED

23 June 1999

TITLE OF INVENTION

APPARATUS AND PROCESS FOR THE DERIVATION OF SHAPED ARTICLES

APPLICANT(S) FOR DO/EO/US


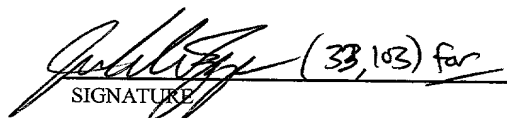
MULLER, Egbert, et al.

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. ☒ This is a **FIRST** submission of items concerning a filing under 35 U.S.C. §371.
2. ☐ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. §371.
3. ☐ This express request to begin national examination procedures (35 U.S.C. §371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. §371(b) and PCT Articles 22 and 39(1).
4. ☒ A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.
5. ☒ A copy of the International Application as filed (35 U.S.C. §371(c)(2))
 - a. ☐ is transmitted herewith (required only if not transmitted by the International Bureau).
 - b. ☒ has been transmitted by the International Bureau.
 - c. ☐ is not required, as the application was filed in the United States Receiving Office (RO/US).
6. ☒ A translation of the International Application into English (35 U.S.C. §371(c)(2)).
7. ☒ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. §371(c)(3))
 - a. ☐ are transmitted herewith (required only if not transmitted by the International Bureau).
 - b. ☐ have been transmitted by the International Bureau.
 - c. ☐ have not been made; however, the time limit for making such amendments has NOT expired.
 - d. ☒ have not been made and will not be made.
8. ☐ A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. §371(c)(3)).
9. ☒ An oath or declaration of the inventor(s) (35 U.S.C. §371(c)(4)).
10. ☐ A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. §371(c)(5)).

Items 11. to 16. below concern document(s) or information included:

11. ☐ An Information Disclosure Statement under 37 C.F.R. §§1.97 and 1.98.
12. ☐ An assignment document for recording. A separate cover sheet in compliance with 37 C.F.R. §§3.28 and 3.31 is included.
13. ☒ A **FIRST** preliminary amendment.
- ☐ A **SECOND** or **SUBSEQUENT** preliminary amendment.
14. ☐ A substitute specification.
15. ☐ A change of power of attorney and/or address letter.
16. ☐ Other items or information:

U.S. APPLICATION NO. (if known, see 37 CFR 1.51) 10/018482		INTERNATIONAL APPLICATION NO. PCT/EP00/05456		ATTORNEY'S DOCKET NUMBER MERCK 2338	
17. <input checked="" type="checkbox"/> The following fees are submitted: BASIC NATIONAL FEE (37 CFR §1.492 (a) (1) - (5)): Search Report has been prepared by the EPO or JPO..... \$890.00 International preliminary examination fee paid to USPTO (37 CFR §1.482)..... \$710.00 No international preliminary examination fee paid to USPTO (37 CFR §1.482) but international search fee paid to USPTO (37 CFR §1.445(a)(2))..... \$740.00 Neither international preliminary examination fee (37 CFR §1.482) nor international search fee (37 CFR §1.445(a)(2)) paid to USPTO..... \$1040.00 International preliminary examination fee paid to USPTO (37 CFR §1.482) and all claims satisfied provisions of PCT Article 33(2)-(4)..... \$100.00 ENTER APPROPRIATE BASIC FEE AMOUNT =				CALCULATIONS PTO USE ONLY	
				\$890.00	
Surcharge of \$130.00 for furnishing the oath or declaration later than months from the earliest claimed priority date (37 C.F.R. §1.492(e)). <input type="checkbox"/> 20 <input type="checkbox"/> 30					
CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE		
Total claims	4 - 20 =	0	x \$ 18.00	\$0.00	
Independent claims	1 - 3 =	0	x \$ 84.00	\$0.00	
MULTIPLE DEPENDENT CLAIM(S) (if applicable)			+ \$ 280.00		
TOTAL OF ABOVE CALCULATIONS =				\$890.00	
Reduction of 1/2 for filing by small entity, if applicable. A Verified Small Entity Statement must also be					
SUBTOTAL =				\$890.00	
Processing fee of \$130.00 for furnishing the English translation later than months from the earliest claimed priority date (37 C.F.R. §1.492(f)). <input type="checkbox"/> 20 <input type="checkbox"/> 30					
TOTAL NATIONAL FEE =				\$890.00	
Fee for recording the enclosed assignment (37 C.F.R. §1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 C.F.R. §§3.28, 3.31). \$40.00 per property.					
TOTAL FEES ENCLOSED =				\$890.00	
				Amount to be refunded:	
				charged:	
a. <input checked="" type="checkbox"/> A check in the amount of <u>\$890.00</u> to cover the above fees is enclosed. b. <input type="checkbox"/> Please charge my Deposit Account No. <u>13-3402</u> in the amount of \$_____ to cover the above fees. A duplicate copy of this sheet is enclosed. c. <input checked="" type="checkbox"/> The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. <u>13-3402</u> . A duplicate copy of this sheet is enclosed.					
NOTE: Where an appropriate time limit under 37 C.F.R. §§1.494 or 1.495 has not been met, a petition to revive (37 C.F.R. §1.137(a) or (b)) must be filed and granted to restore the application to pending status.					
SEND ALL CORRESPONDENCE TO: Customer Number 23,599					
 23599 PATENT TRADEMARK OFFICE			 SIGNATURE <u>Anthony J. Zelano</u> NAME <u>27,969</u> REGISTRATION NUMBER		
Filed: 19 DECEMBER 2001 AJZ:kmo					

IN THE UNITED STATES DESIGNATED/ELECTED OFFICE

International Application No. : PCT/EP00/05456
International Filing Date : 14 JUNE 2000
Priority Date(s) Claimed : 23 JUNE 1999
Applicant(s) (DO/EO/US) : MULLER, Egbert, et al.

Title: APPARATUS AND PROCESS FOR THE DERIVATION OF SHAPED ARTICLES

PRELIMINARY AMENDMENT

Commissioner for Patents
Washington, D.C. 20231

SIR:

Prior to calculating the national fee, and prior to examination in the National Phase of the above-identified International application, please amend as follows:

IN THE CLAIMS:

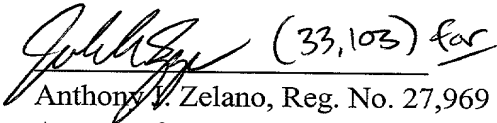
2. (Amended) Process according to Claim 1, characterised in that, in addition, at least one further reaction stage is carried out by the sequence according to claim 1.
3. (Amended) Apparatus for carrying out the process according to Claim 1, comprising a reactor (1), the temperature of which can be controlled via a heat-exchange device (3), one or more stock vessels (4), which are connected to the reactor via one or more feed lines with pumps (5), one or more heat exchangers (6) for pre-setting of the temperature of the solutions, an outflow (7) from the reactor, which is connected in such a way that solutions can be subjected to cyclic and through-pumping, and a control device for control of the process steps.

REMARKS

The purpose of this Preliminary Amendment is to eliminate multiple dependent claims in order to avoid the additional fee. Applicants reserve the right to reintroduce claims to canceled combined subject matter.

Attached hereto is a marked-up version of the changes made to the claims by the current amendment. The attached pages are captioned "**Version With Markings to Show Changes Made**".

Respectfully submitted,

 (33,103) *for*

Anthony V. Zelano, Reg. No. 27,969

Attorney for Applicants

MILLEN, WHITE, ZELANO & BRANIGAN, P.C.

Arlington Courthouse Plaza 1

2200 Clarendon Boulevard, Suite 1400

Arlington, VA 22201

Direct Dial: 703-812-5311

Facsimile: 703-243-6410

Email: zelano@mwzb.com

AJZ;kmo

Filed: 19 DECEMBER 2001

VERSION WITH MARKINGS TO SHOW CHANGES MADE

Claims 2 and 3 were amended as follows:

2. (Amended) Process according to Claim 1, characterised in that, in addition, at least one further reaction stage is carried out by the sequence according to ~~Claim 1 or 2~~ claim 1 or 2.

3. (Amended) Apparatus for carrying out the process according to ~~one of Claims 1 and 2~~, comprising a reactor (1), the temperature of which can be controlled via a heat-exchange device (3), one or more stock vessels (4), which are connected to the reactor via one or more feed lines with pumps (5), one or more heat exchangers (6) for pre-setting of the temperature of the solutions, an outflow (7) from the reactor, which is connected in such a way that solutions can be subjected to cyclic and through-pumping, and a control device for control of the process steps.

Apparatus and process for the derivatization of shaped articles

The invention relates to a process for the derivatization of shaped articles with covalently bonded polymers, and to an apparatus for carrying out this process.

The literature discloses various support materials which have been derivatised with covalently bonded polymers. The derivatisation here can be carried out via a number of steps, for example condensation reactions or free-radical reactions. Block or graft polymers can be formed.

The derivatisations are usually carried out in a batch process, as, for example, in DE 43 10 964 and EP 0 337 144, which describe the derivatisation of hydroxyl-containing supports with methacrylic acid derivatives, allyl-amines, etc., with catalysis by cerium(IV) salts. In these processes, the support to be derivatised is stirred continuously in the reaction solution throughout the reaction duration or the solutions are subjected to cyclic or through pumping throughout the reaction duration.

The patent applications DE 195 01 726, WO 96/22316 and DE 196 24 813 disclose polymerisable derivatives of polyamides and processes for polymerisation onto polyamides derivatised in this way. The shaped article to be modified is derivatised in an externally heatable reaction tube, with the polymer being brought to reaction with the monomer, and the reaction solution is constantly subjected to cyclic or through pumping with heating.

The way in which the reaction during the individual reaction steps, especially that of the attachment by polymerisation, is of crucial importance for the quality of the polymers obtained. The derivatised shaped articles formed often exhibit an inhomogeneous distribution of the attached polymer. Furthermore, filtration effects in the fibre structure of porous

shaped articles or membranes cause an increase in the content of homopolymer, which can only be removed with difficulty.

5 The object is thus to develop a process which enables the production of derivatised shaped articles having a high and uniform degree of polymerisation. A further object is to reduce the accumulation of homopolymer in porous shaped articles.

10 It has been found that performance of the reaction in a modified way results in significant improvements with respect to the degree of polymerisation and uniform spatial distribution of the polymer. Whereas the reaction solution is subjected to cyclic or through pumping throughout the reaction duration, including the heating phase, in the processes from the prior art, the quality of the products increases considerably if the flow is interrupted
15 after equilibration of the reaction space with the reaction solution and the reaction mixture is heated externally and brought to reaction without further pumping.

20 The invention therefore relates to a process for the derivatisation of shaped articles, comprising a polymerisation stage and optional pre-reactions and polymer-analogous reactions, where at least one of the reaction stages comprises the following reaction steps:

- 25
- a) equilibration of the reaction space with the reaction solution,
 - b) maintenance of the reaction space at a temperature which is lower than or equal to the threshold temperature,
 - c) optional heating to the threshold temperature,
 - d) switching off of the flow,
 - e) heating of the reaction space to the reaction temperature.

30 In a preferred embodiment, one or more further steps are additionally carried out by the process according to the invention.

The invention also relates to an apparatus for carrying out the process according to the invention, comprising a reactor with heat-exchange device, one or more stock vessels, which are connected to the reactor via one or more feeds with pumps and/or valves, one or more heat exchangers for pre-heating the solutions, an outlet from the reactor, and preferably a control or regulation device for control of the process steps. The reactor, outlet and collection vessel as well as the stock vessels are provided with valves which allow solutions to be subjected to cyclic or through pumping.

A preferred embodiment of the apparatus comprises two or more reactors connected in parallel via distributors.

Figure 1 shows a reaction plant according to the invention with jacketed reactor.

Figure 2 shows a distributor head for a plant having six reactors.

Porous and nonporous shaped articles which are suitable as base polymer are known to the person skilled in the art and are in some cases also commercially available.

These include, for example, the polymers known under the trade name NYLON®, for example NYLON® 66 and NYLON® 6.

Base polymers according to the invention are also base supports having functional groups, such as primary or secondary aliphatic hydroxyl groups, such as, for example, crosslinked or uncrosslinked polysaccharides based on agarose or cellulose and derivatives thereof, furthermore polymers based on dextran, and other polymers, as disclosed, for example, in DE 43 10 964.

Porous or nonporous shaped articles consisting of base polymers of this type are, in accordance with the invention, for example bead-shaped shaped articles, membranes, hoses, hollow-fibre membranes, spiral membranes, sponges, gel particles, ceramic shaped articles, or polymer mats, such as, for example, cellulose mats.

In the derivatisation of polyamidic shaped articles with covalently bonded polymers, unsaturated radicals are typically introduced into the polyamide in the first reaction step. To this end, reaction sequences known from DE 195 01 726 and DE 196 24 813 can be used. It is common to these reaction sequences that an ethylenically unsaturated derivatising agent, i.e. an amino- or carboxyl-reactive compound containing a polymerisable double bond, is brought to reaction with the amino or carboxyl groups of the polyamide. Amino-reactive compounds, such as, for example, glycidyl methacrylate or vinylazlactone derivatives, are in principle known to the person skilled in the art in large number and are revealed, for example, in DE 195 01 726 and DE 196 24 813. Analogously, it is possible to derivatise the free carboxyl groups of polyamides so that they are likewise available as reactive group for a polymerisation. To this end, compounds which are able to react with carboxyl groups and which contain polymerisable double bonds, for example allylamine, can be used.

If the base polymer contains both carboxyl and amino groups, it is possible, as disclosed in DE 196 24 813, to increase the loading density by carrying out a reaction with a bifunctional derivatising agent, i.e. with a diamino compound or with a dicarboxylic acid or a dicarboxylic anhydride, before the reaction with the ethylenically unsaturated derivatising agent. Thus, for example, reaction with 1,2-ethylenediamine enables additional amino groups to be introduced into the base polymer, which groups can then be reacted further as described above. Preferred diamino compounds are, in particular, α,ω -diaminoalkanes, such as, for example, 1,2-ethylenediamine, 1,3-diaminopropane, 1,4-diaminobutane or 1,6-diaminohexane. It is like-

wise possible to react the amino groups of the polyamide with a dicarboxylic acid or a dicarboxylic anhydride in order subsequently to introduce polymerisable double bonds at the carboxyl groups.

5 After introduction of the polymerisable double bond, the polymerisation of monomers is carried out at the double bond, giving a block polymer which contains any the functional groups introduced with the monomers. Monomers according to the invention are building blocks as disclosed in DE 195 01 726 and DE 196 24 813.

10 For the production of shaped articles having defined properties, the monomers attached by polymerisation may carry certain functional groups, in accordance with the invention also separation effectors. In accordance with the invention, separation effectors may equally be bound in a further
15 reaction step after the block polymerisation to reactive groups introduced via the monomers. Separation effectors, such as, for example, ionic groups, such as sulfonic or carboxylic acid groups, substituted amines, hydrophobic groups, metal chelate groups, thiophilic radicals, chiral radicals or functionalities for binding enzymes or antibodies, are known in large number to the
20 person skilled in the art and are disclosed, for example, in DE 195 01 726 and DE 196 24 813.

The derivatised and polymer-modified shaped articles according to the invention which contain separation effectors on the polymerised-on chains
25 can be employed in a similar manner for substance separations or as ion exchangers, as is usual, for example, for particulate sorbents with similar separation effectors.

30 Reaction sequences for the said reactions are known to the person skilled in the art.

The polyamides preferably used, such as, for example, NYLON[®] 66 or NYLON[®] 6, contain only terminal free carboxyl and/or amino groups. In this case, the polymerisation with monomers onto the derivatised base polymer gives a block polymer. If the base polymer contains pendant lateral free carboxyl and/or amino groups in addition to the terminal free carbonyl and/or amino groups, pendant polymerisable groups are additionally formed. In a subsequent polymerisation, grafting then takes place in addition to the formation of the block polymer. Block and graft polymers are collectively referred to in accordance with the invention as polymer-modified base polymers or polymer-modified materials. Block and graft polymerisation are collectively referred to according to the invention as attachment by polymerisation.

The inventive teaching can basically be applied to all processes in which monomeric building blocks are polymerised onto a support, it being possible for both block and graft polymers to be formed. This includes, for example, graft polymerisation onto supports containing hydroxyl groups in which cerium(IV) is employed as catalyst.

The way in which the process according to the invention is carried out for the derivatisation of polyamides is explained in greater detail below by way of example.

The discontinuous process according to the invention for the preparation of polymer-modified base polymers can be employed for all described stages of the reaction sequences, i.e.

- in pre-reactions carried out before the attachment by polymerisation and serving, for example,
 - for increasing the density of the derivatisable functional groups,
 - for the derivatisation of functional groups of a base support with compounds containing a polymerisable double bond,
- in the attachment by polymerisation,

- in polymer-analogous reactions, such as further modifications and introduction of separation effectors after the attachment by polymerisation.

The various stages of the reaction sequence are referred to in accordance with the invention as reaction stages. The compositions of the reaction solutions required for the individual reaction stages are known to the person skilled in the art from processes as disclosed, for example, in DE 195 01 726, WO 96/22316 and DE 196 24 813.

The performance of the reaction in accordance with the invention produces the greatest advantage in attachment by polymerisation, where it is possible for the first time both to achieve a high and homogeneous degree of polymerisation and to maintain the permeability of porous shaped articles.

Particularly in the case of inhomogeneous shaped articles, however, advantages can be achieved in each reaction stage by the process according to the invention. Due to the rapid cyclic pumping of the reaction solution and the careful equilibration of the reaction space, a similar concentration of the reaction solution exists at each point of the shaped article. This ensures a homogeneous distribution of the reactants in the reaction phase, in which, due to interruption of the flow, this state is no longer changed, and thus ensures a homogeneous product. If, by contrast, pumping is also carried out during the reaction phase, a different distribution of the reaction solution in the shaped article may occur during the reaction, with the consequence of inhomogeneous covering of the shaped article with the reaction product. This aspect suggests that the reaction in accordance with the invention be performed in the other reaction steps in addition to the polymerisation.

Typically, therefore, optional reaction stages preceding or succeeding the attachment by polymerisation, referred to in accordance with the invention as pre-reactions or polymer-analogous reactions, are equally carried out by the process according to the invention as the polymerisation itself. How-

ever, it is just as possible to carry out one or more of the reaction stages by other methods, for example with constant pumping.

5 The process according to the invention is carried out in a reaction plant according to the invention. Figure 1 shows an example of an apparatus according to the invention for carrying out the process. The heart of the plant is a reactor (1). In its preferred design, the reactor is tubular with a length of from 10 to 100 cm and a diameter of from 2 to 90 cm. This design serves for the derivatisation of shaped articles which can be introduced into the reactor without further auxiliaries. In the case of other shaped articles, such as, for example, wound flat membranes with spacers, holding devices or corresponding recesses can be incorporated into the reactor. Since temperature control is necessary during the reactions, the reactor (1) is provided with a heat-exchange device. This is preferably a double-walled jacket (2), which can be temperature-controlled by an attached heat exchanger (3). Other methods for temperature control are also known to the person skilled in the art, i.e. other reactor forms in which heat exchangers are installed or to which they are connected. Furthermore, the plant according to the invention is not restricted only to a single reaction vessel. 10 Through the necessity for a heat-exchange device, the reactors cannot be enlarged to any desired extent, since otherwise the heat exchange only takes place with inadequate speed. In accordance with the invention, however, the throughput of the plant can be greatly increased by addressing up to, for example, 12 reactors in parallel via suitable distributors. The distributors, which facilitate parallel, uniform inflow and outflow of the solutions into and out of the individual reactors, are typically connected to the reactors via short pieces of pipe or hoses. Similar distributors control the inflow and outflow of liquid into and out of the heat exchangers surrounding the individual reactors. The term reactor or reactor tube therefore also means in accordance with the invention both an 15 individual reactor and a plurality of reactors or reaction tubes connected in parallel. 20 25 30

Connected to the reaction tube (1) are one or more stock containers (4), from which reaction solutions or washing solutions can be pumped into the reactor via feed lines by means of one or more pumps (5). The feed line to the reaction tube is preferably provided with a second heat exchanger (6), so that the solutions have already been subjected to temperature control before being pumped into the reactor. Furthermore, the reactor has an outflow (7). In the case of through-pumping of a solution, this leads into a waste vessel (8), and in the case of cyclic pumping, it leads back into the feed line to the reactor. Control of the individual reaction steps, i.e. the temperature, flow rate, feed of the reaction solutions, etc., can take place manually or automatically via an integrated control device. Control mechanisms and control devices which enable such control are known to the person skilled in the art. In order to take into account the way in which the reaction is carried out in the process according to the invention, all pumps and valves which serve for transport and mixing of the requisite reaction solutions must be capable of very flexible control. For example, it must be possible to achieve the following operational states:

- cyclic pumping through the reactor
- cyclic pumping through the reactor including a heat exchanger
- cyclic pumping through the reactor including a stock vessel
- pumping of one or more reagents through the reactor
- pumping through the reactor and into the waste
- stopping of through-pumping or cyclic pumping.

These operational states are possible, for example, using devices as shown in Figure 1 and obvious variants of this device. To this end, the pumps and valves must be capable of parallel or independent operation. In addition, it must be possible to operate different valves in parallel or independently for respectively through-pumping or cyclic pumping of the solutions.

Figure 2 shows a distributor head for the parallel addressing of 6 reactors. Part-figure A shows a side view and part-figure B a section through the distributor head along plane E.

In the process according to the invention, various reaction steps or phases are passed through during the individual reaction stages. Firstly, the shaped article located in the reactor is saturated with the reaction solution. This is carried out by rapid cyclic pumping or through-pumping of the reaction solution. In the case of cyclic pumping, the reaction solution is recycled after flowing through the reactor and is pumped through the reactor again; in the case of through-pumping, the reaction solution is discarded after flowing through the plant once. In accordance with the invention, the saturation of the reaction space, i.e. the reactor containing the shaped article, with the reaction solution and further reaction steps, such as prior temperature control of the reaction solution, can be carried out by cyclic pumping or through-pumping of the reaction solution or a combination of the two possibilities. The reaction solution is preferably pumped through the reactor at a linear flow rate of 2–100 cm/min during the saturation phase of about 3–30 min. This is referred to in accordance with the invention as rapid through-pumping and corresponds approximately to through-flow of 5 bed volumes, which guarantees a homogeneous distribution of the reaction solution in the reaction space. The duration and flow rate during the mixing phase can, however, also be varied beyond the stated values, depending on the application.

After saturation of the reactor with the monomer solution, either the flow is interrupted directly by switching off the pump, or, preferably, the pump is set to recycle. During this cyclic pumping phase, the temperature of the reaction solution is pre-set by means of the heat exchanger (6). The temperature in this phase is preferably below the threshold temperature, at which the reaction rate is only up to 1/10 of the rate during the actual reaction. The reason for this is that the reaction should only commence after the reaction space has been equilibrated and the flow has been switched off. Pre-setting of the temperature during the cyclic pumping enables faster heating after the flow has been switched off. This procedure is particularly important during the attachment by polymerisation, where the

temperature during the pre-setting of the temperature must not be selected so high that thermally initiated free-radical decomposition takes place, otherwise homopolymerisation of the monomers would occur even before entry into the reactor, and thus undefined reaction conditions and filtration effects would arise. The threshold temperature on use of 2,2'-azoisobutyronitrile (AIBN) should therefore be set, for example, at about 60°C. Table 1 shows that the half-value time of azoisobutyronitrile at 60°C is about 21 hours. During a warm-up phase of half an hour, 1.2% of the AIBN would thus decompose.

Temperature [°C]	Half-value time [h]
37	962.5
43	275
50	96.25
60	21.15
100	0.12

Tab. 1 Half-value times for the thermal decomposition of AIBN

In accordance with the invention, the saturation of the reaction space with the reaction solution and the optional subsequent pre-setting of the temperature of the reaction solution up to the threshold temperature are referred to as equilibration of the reaction space. After the equilibration, the flow is interrupted in accordance with the invention, and the mixture is brought to the reaction temperature externally by temperature control of the jacket by means of heat exchanger (3). The reaction temperature depends on the type of reaction and is known to the person skilled in the art from other processes. Performance of the reaction in this way keeps the concentration of the monomers constant in time and space during the polymerisation, and a local increase in the concentration of homopolymer does not occur. After the reaction, the reaction solution is pumped off, and the reactor is flushed with corresponding solvents.

The polymers obtained by the process according to the invention have a high and uniform degree of polymerisation. The permeability of membranes and capillaries is not changed to a significant extent on derivatisation using this process.

5

Even without further comments, it is assumed that a person skilled in the art will be able to utilise the above description in the broadest scope. The preferred embodiments and examples should therefore merely be regarded as descriptive disclosure which is absolutely not to be regarded as limiting in any way.

10

The complete disclosure content of all applications, patents and publications mentioned above and below and of corresponding application DE 199 28 719, filed June 23, 1999, is incorporated into this application by way of reference.

15

Example

20

Reaction sequence for the preparation of a weak anion exchanger (DEA type)

Packing of the reaction tube

25

Two polyamide bundles with capillaries bent in a hairpin shape are packed into the reaction tube. These are type 386c polyamide fibres from Membrana GmbH with an external diameter of 520 μm and an internal diameter of 300 μm . The mean pore width is 0.4 μm . With maximum space filling, about 5890 capillaries can be packed per bundle. For a length of 138 mm per bundle and a membrane porosity of about 60%, the membrane volume is 230 ml.

30

Derivatisation of the amino end groups of the polyamide using glycidyl methacrylate

187 g of epoxypropyl methacrylate and 330 g of sodium hydroxide solution (32%) are dissolved in 2250 ml of water and 750 ml of 1,4-dioxane. This solution is pumped through the reactor for 3 minutes at a flow rate of 600 ml/min. The pump is then switched to recycle. The reaction solution is brought to a temperature of 42°C by the heat exchanger (6). The pump is switched off and left to stand for 1.5 hours at a water jacket temperature of 55°C. The mixture is subsequently washed with 3.5 litres of each of water, acetone and toluene.

Block polymerisation using glycidyl methacrylate

570 g of epoxypropyl methacrylate and 18.7 g of azoisobutyronitrile are dissolved in 3300 ml of toluene. This solution is pumped through the reactor for 3 minutes at a flow rate of 600 ml/min. The pump is then switched to recycle. The reaction solution is brought to a temperature of 60°C by the heat exchanger (6). The pump is switched off and left to stand for 2 hours at a water jacket temperature of 93°C. The mixture is subsequently washed with 3.5 litres of each of water, acetone and toluene.

Reaction of the epoxy groups with diethylamine

A solution of 1.5 l of diethylamine in 1.5 l of water is pumped through the reactor for 3 minutes at a flow rate of 600 ml/min. The pump is then switched to recycle. The reaction solution is brought to a temperature of 65°C by the heat exchanger (6). The pump is switched off and left to stand for 3 hours at a water jacket temperature of 65°C. The mixture is subsequently washed with 4 litres of water.

Improvement in biocompatibility

A solution of 750 ml of ethanolamine in 3000 ml of water is pumped through the reactor for 4 minutes at a flow rate of 600 ml/min. The pump is then switched to recycle. The reaction solution is brought to a temperature of

44°C by the heat exchanger (6). The pump is switched off and left to stand for 2.5 hours at a water jacket temperature of 60°C. The mixture is subsequently washed with 3.5 litres of each of water, 1M sodium hydroxide solution and ethanol and dried under reduced pressure.

The initial mass of the membrane material was 66 g. After the modification, the material had a mass of 100 g, which corresponds to an increase in mass of 51% relative to the mass of the starting polymer.

In order to investigate the uniformity of the coating, test segments (in each case 64 capillaries, 101 mm in length) were taken from different areas of the membrane mats.

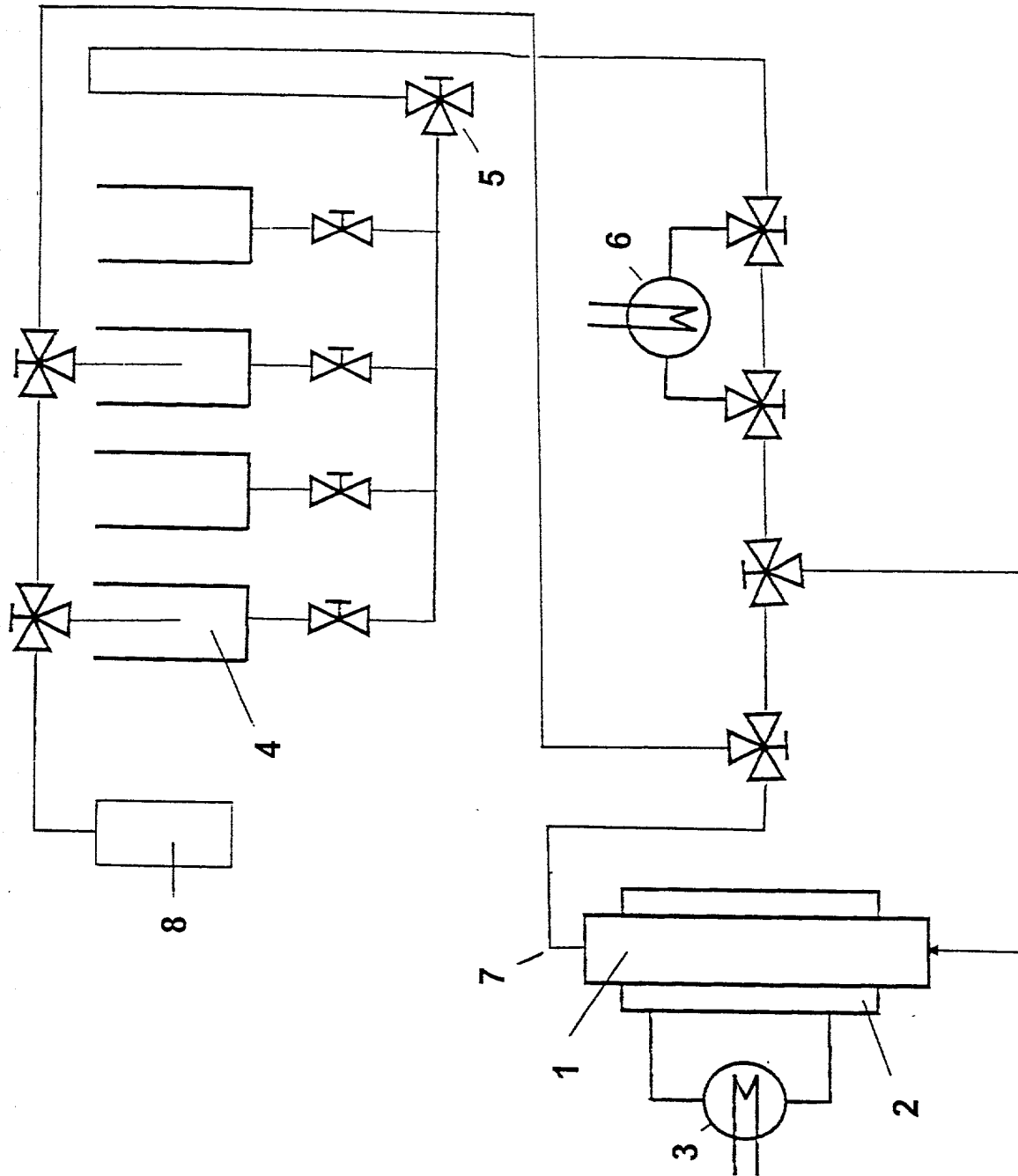
Membrane position in reaction tube	Mass after modification [g]
1st bundle outer layer	0.38
1st bundle middle	0.37
1st bundle core	0.37
2nd bundle outer layer	0.38
2nd bundle middle	0.37
2nd bundle core	0.37

A very uniform distribution of the coating on the polymer is thus obtained.

Claims

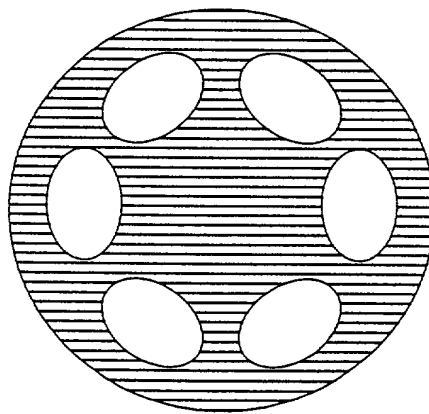
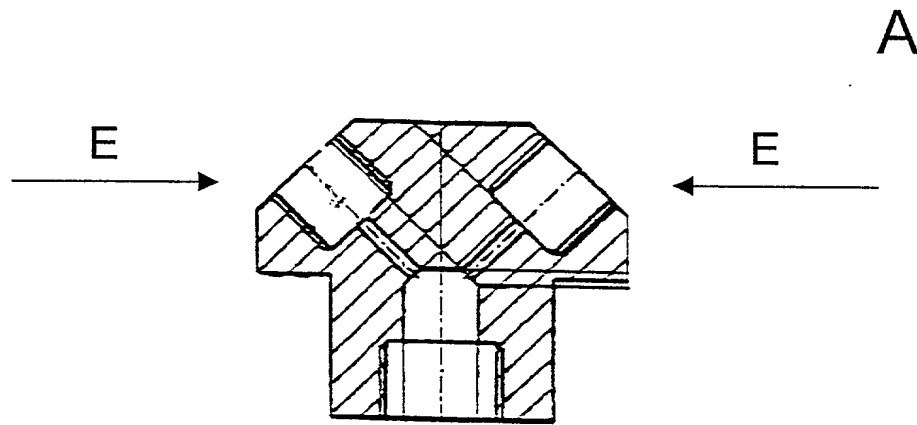
1. Process for the derivatisation of shaped articles, comprising a polymerisation stage and optional pre-reactions and polymer-analogous reactions, characterised in that at least one reaction stage comprises the following reaction steps:
- a) equilibration of the reaction space with the reaction solution,
 - b) maintenance of the reaction space at a temperature which is lower than or equal to the threshold temperature,
 - c) optional heating to the threshold temperature,
 - d) switching off of the flow,
 - e) heating of the reaction space to the reaction temperature.
2. Process according to Claim 1, characterised in that, in addition, at least one further reaction stage is carried out by the sequence according to Claim 1 or 2.
3. Apparatus for carrying out the process according to one of Claims 1 and 2, comprising a reactor (1), the temperature of which can be controlled via a heat-exchange device (3), one or more stock vessels (4), which are connected to the reactor via one or more feed lines with pumps (5), one or more heat exchangers (6) for pre-setting of the temperature of the solutions, an outflow (7) from the reactor, which is connected in such a way that solutions can be subjected to cyclic and through-pumping, and a control device for control of the process steps.
4. Reaction plant according to Claim 3, characterised in that two or more reactors can be addressed in parallel via distributors.

Fig. 1



2/2

Fig. 2



Docket No.
Merck

Declaration and Power of Attorney For Patent Application English Language Declaration

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name,

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled

Apparatus and process for the derivatization of shaped articles

the specification of which

(check one)

- ☐ is attached hereto.
☒ was filed on 14.06.2000 as United States Application No. or PCT International Application Number PCT/EP00/05456 and was amended on _____ (if applicable)

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose to the United States Patent and Trademark Office all information known to me to be material to patentability as defined in Title 37, Code of Federal Regulations, Section 1.56.

I hereby claim foreign priority benefits under Title 35, United States Code, Section 119(a)-(d) or Section 365(b) of any foreign application(s) for patent or inventor's certificate, or Section 365(a) of any PCT International application which designated at least one country other than the United States, listed below and have also identified below, by checking the box, any foreign application for patent or inventor's certificate or PCT International application having a filing date before that of the application on which priority is claimed.

Prior Foreign Application(s)

Priority Not Claimed

199 28 719.8 Germany 23.06.1999
(Number) (Country) (Day/Month/Year Filed)

☐

(Number) (Country) (Day/Month/Year Filed)

☐

(Number) (Country) (Day/Month/Year Filed)

☐

I hereby claim the benefit under 35 U.S.C. Section 119(e) of any United States provisional application(s) listed below:

(Application Serial No.)

(Filing Date)

(Application Serial No.)

(Filing Date)

(Application Serial No.)

(Filing Date)

I hereby claim the benefit under 35 U.S.C. Section 120 of any United States application(s), or Section 365(c) of any PCT International application designating the United States, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT International application in the manner provided by the first paragraph of 35 U.S.C. Section 112. I acknowledge the duty to disclose to the United States Patent and Trademark Office all information known to me to be material to patentability as defined in Title 37, C.F.R., Section 1.56 which became available between the filing date of the prior application and the national or PCT International filing date of this application:

(Application Serial No.)

(Filing Date)

(Status)
(patented, pending, abandoned)

(Application Serial No.)

(Filing Date)

(Status)
(patented, pending, abandoned)

(Application Serial No.)

(Filing Date)

(Status)
(patented, pending, abandoned)

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

POWER OF ATTORNEY: As a named inventor, I hereby appoint

I. William Millen (Reg. No. 19,544)

John L. White (Reg. No. 17,746)

Anthony J. Zelano (Reg. No. 27,969)

Alan E.J. Branigan (Reg. No. 20,565)

John R. Moses (Reg. No. 24,983)

Harry B. Shubin (Reg. No. 32,004)

Brion P. Heaney (Reg. No. 32,542)

Richard J. Traverso (Reg. No. 30,595)

John A. Sopp (Reg. No. 33,103)

Richard M. Lebovitz (Reg. No. 37,067)

John H. Thomas (Reg. No. 33,460)

Catherine M. Joyce (Reg. No. 40,668)

James T. Moore (Reg. No. 35,619)

James E. Ruland (Reg. No. 37,432)

Nancy Axelrod (Reg. No. 44,014)

Jennifer J. Branigan (Reg. No. 40,921)

to prosecute this application and transact all business in the Patent and Trademark Office connected therewith.

Send Correspondence to: MILLEN; WHITE; ZELANO & BRANIGAN, P.C.

Arlington Courthouse Plaza I

2200 Clarendon Blvd., Suite 1400

Arlington, VA 22201

Direct Telephone Calls to: (name and telephone number)

Full name of sole or first inventor	
Egbert Müller	24.10.01
Sole or first inventor's	Date
Residence	
Im Erlich 10, 64291 Darmstadt, Germany	DEX
Citizenship	
German	
Post Office Address	
c/o Merck KGaA, Frankfurter Str. 250, 64293 Darmstadt, Germany	

Full name of second inventor, if any	
Thomas Heil	24.10.01
Second inventor's signature	Date
Residence	
Frankfurter Straße 5, 64572 Büttelborn, Germany	DEX
Citizenship	
German	
Post Office Address	
c/o Merck KGaA, Frankfurter Str. 250, 64293 Darmstadt, Germany	